MULTIBLOCK BIODEGRADABLE HYDROGELS FOR DRUG DELIVERY AND TISSUE TREATMENT

This application is a provision of U.S. Ser. No. 60/001,723, filed Jul. 28, 1995.

BACKGROUND OF THE INVENTION

The present invention is generally in the area of biodegradable polymers for use in drug delivery and biomedical applications.

Biodegradable polymers have been developed for use in a variety of surgical and drug delivery applications. The synthesis and biodegradability of poly(lactic acid) was reported by Kulkarni et al., *Arch. Surg.,* 93:839 (1966). Biodegradable polyanhydrides and polyorthoesters having labile backbone linkages have been developed. Domb et al., *Macromolecules,* 22:3200 (1989); and Heller et al., "Biodegradable Polymers as Drug Delivery Systems," Chasin, M. and Langer, R., Eds., Dekker, New York, 121–161 (1990), the disclosures of which are incorporated herein. Polymers which degrade into naturally occurring materials, such as polyaminoacids, also have been developed. Polyesters of α-hydroxy acids, such as lactic acid or glycolic acid, are widely used as biodegradable materials for applications ranging from closure devices, including sutures and staples, to drug delivery systems. Holland et al., *Controlled Release,* 4:155–180, (1986); U.S. Pat. No. 4,741,337 to Smith et al; and Spilizewski et al., *J. Control. Rel.,* 2:197–203 (1985), the disclosures of which are incorporated herein.

Degradable polymers containing water-soluble polymer elements have been described. Degradable polymers have been formed by copolymerization of lactide, glycolide, and ϵ-caprolactone with the polyether, polyethylene glycol ("PEG"), to increase the hydrophilicity and degradation rate. Sawhney et al., *J. Biomed. Mater. Res.* 24:1397–1411 (1990). U.S. Pat. No. 4,716,203 to Casey et al. describes the synthesis of a block copolymer of PGA (poly(glycolic acid)) and PEG. U.S. Pat. No. 4,716,203 to Casey et al. describes the synthesis of PGA-PEG diblock copolymers.

Polymers formed from crosslinkable monomers or prepolymers have been developed in the prior art. Crosslinked hyaluronic acid has been used as a degradable swelling polymer for biomedical applications. U.S. Pat. Nos. 4,987,744 and 4,957,744 to Della Valle et al.; and Della Valle et al., *Polym. Mater. Sci. Eng.,* 62:731–735 (1991).

U.S. Pat. No. 5,410,016 to Hubbell et al., the disclosure of which in incorporated herein, discloses the in situ crosslinking of biodegradable, water-soluble macro-monomers, ("macromers") to form barrier coatings and matrices for delivery of biologically active agents. Other polymers for drug delivery or other biomedical applications are described in U.S. Pat. No. 4,938,763 to Dunn, U.S. Pat. Nos. 5,160,745 and 4,818,542 to DeLuca, U.S. Pat. No. 5,219,564 to Zalipsky, U.S. Pat. No. 4,826,945 to Cohn, and U.S. Pat. Nos. 5,078,994 and 5,429,826 to Nair, the disclosures of which are incorporated herein by reference. Methods for delivery of the polymers materials include syringes (U.S. Pat. No. 4,938,763 to Dunn et al.) spray applicators (WO 94/21324 by Rowe et al.) and catheter delivery systems (U.S. Pat. Nos. 5,328,471; and 5,213,580 to Slepian). The synthesis of macromers including a central chain of polyethylene glycol, with an oligomeric hydroxyacid at each end and acrylic esters at the ends of the hydroxy acid oligomer also has been reported. Sawhney A. S. et al., *Macromolecules,* 26: 581 (1993); and PCT WO 93/17669 by Hubbell J. A. et al., the disclosures of which are incorporated herein by reference.

Thermal volume changes in polymeric gels, such as esters and amides of polyacrylic acid, have been described. For example, poly(N-isopropyl acrylamide) based hydrogels, which are thermosensitive in aqueous systems, have been used for controlled drug delivery and other applications. U.S. Pat. No. 5,403,893 to Tanaka et al.; and Hoffman A. S. et al., *J. Controlled Release,* 6:297 (1987), the disclosures of which are incorporated herein. Poly(N-isopropyl acrylamide), however, is non-degradable and is not suitable for applications where biodegradable polymers are required. Non-biodegradable polymeric systems for drug delivery are disadvantageous since they require removal after the drug-polymer device is implanted.

It is an object of the invention to provide improved polymer systems for use in drug delivery and other biomedical applications such as surgical applications. It is an additional object of the invention to provide polymer systems for use in controlled drug delivery which are capable of releasing a biologically active agent in a predictable and controlled rate. It is a further object of the invention to provide polymers for use in controlled drug delivery which release the active agent locally at a particular targeted site where it is needed. It is another object of the invention to provide polymer systems for use in drug delivery which have properties including volume and drug release which are variable with temperature or other parameters such as pH or ion concentration.

SUMMARY OF THE INVENTION

Macromers are provided which are capable of gelling in an aqueous solution. In one embodiment, the macromers include at least four polymeric blocks, at least one of which is hydrophilic and at least two of which are hydrophobic, and include a crosslinkable group. The polymer blocks may be selected to provide macromers with different selected properties. The macromers can be covalently crosslinked to form a gel on a tissue surface in vivo. The gels formed from the macromers have a combination of properties including thermosensitivity and lipophilicity, and are useful in a variety of medical applications including drug delivery and tissue coating.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a scheme showing the different gel states and properties of one embodiment of a thermoresponsive biodegradable macromer formed from a polypropylene oxide-polyethylene oxide block copolymer.

FIG. **2** is a graph of temperature-dependent changes in gel volume of gels formed by photopolymerization of an acrylated polypropylene oxide-polyethylene oxide block copolymer containing a biodegradable region.

FIG. **3** is a graph showing the effects of temperature on dextran release from a gel formed by photopolymerization of an acrylated polypropylene oxide-polyethylene oxide block copolymer.

FIG. **4** is a graph illustrating the variation in the speed of photocrosslinking of acrylated polypropylene oxide-polyethylene oxide block copolymers having incorporated therein different biodegradable regions.

FIG. **5** is a graph showing the in vitro profiles of degradation rate of gels formed by photocrosslinking of acrylated polypropylene oxide-polyethylene oxide block copolymers having incorporated therein different biodegradable regions.